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Resistance in persisting bat populations after white-nose syndrome invasion

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Increases in anthropogenic movement have led to a rise in pathogen introductions and the emergence of infectious diseases in naive host communities worldwide. We combined empirical data and mathematical models to examine changes in disease dynamics in little brown bat (*Myotis lucifugus*) populations following the introduction of the emerging fungal pathogen *Pseudogymnoascus destructans*, which causes the disease white-nose syndrome. We found that infection intensity was much lower in persisting populations than in declining populations where the fungus has recently invaded. Fitted models indicate that this is most consistent with a reduction in the growth rate of the pathogen when fungal loads become high. The data are inconsistent with the evolution of tolerance or an overall reduced pathogen growth rate that might be caused by environmental factors. The existence of resistance in some persisting populations of little brown bats offers a glimmer of hope that a precipitously declining species will persist in the face of this deadly pathogen.

This article is part of the themed issue 'Human influences on evolution, and the ecological and societal consequences'.

1. Introduction

The ability of species to respond to global change is a key determinant of Earth's future biodiversity [1]. Pathogen introductions owing to increased trade and travel threaten human, livestock and wildlife health and are a major conservation challenge in the Anthropocene [2]. Although the impacts of introduced pathogens are well established, and include continental-scale population declines [3,4], species extinctions [5–8], and shifts in community structure and ecosystem function [9–11], the evolutionary response of hosts to introduced pathogens has received far less study [12–14]. Understanding the ability of species to respond to introduced pathogens can help determine whether species will persist or go extinct in the face of disease, and thereby guide management action [15–17].

Outcomes of pathogen introductions include host extinction, host persistence owing to decreasing transmission following population declines (density-dependent effects), and the evolution of mechanisms that allow hosts to cope with disease. Potential mechanisms include resistance, tolerance, evolution of lower pathogen virulence and shifts in life-history traits that can result in demographic compensation [7,18–22]. Host resistance is defined as mechanisms that reduce the growth rate of the pathogen, and thereby reduce host morbidity or mortality. Host tolerance, by contrast, describes traits that enable hosts to reduce disease without reducing the growth rate of the pathogen [18,21]. Evolution of host tolerance and resistance are sometimes antagonistically related, in that evolution of one trait could limit the selective benefit for the other [23]. Host traits conferring tolerance are thought to be more likely to reach fixation

in a population than resistance, because there is no decrease in pathogen transmission, and therefore little decrease in selective pressure on the pathogen, as the frequency of the trait increases in the population [18,24]. By contrast, the evolution of resistance is limited by reduced transmission as resistance becomes common [18]. In addition, there is less selective pressure on the pathogen when hosts evolve tolerance, which reduces the coevolutionary arms race between pathogens and hosts [18]. It has been suggested that populations can undergo shifts in defence systems, either owing to negative frequency-dependent selection or as pathogens change in response to host defences [25]. The introduction of pathogens to novel host communities provides an opportunity to understand the development of coevolutionary dynamics between hosts and pathogens [26].

The fungus *Pseudogymnoascus destructans* was recently introduced to North American bat populations, where it causes the disease white-nose syndrome (WNS) [27–29]. The fungus was first detected in a commercial cave in upstate New York in 2006, and has caused mass mortality of bat populations as it has spread across North America. Several species of bats have been predicted to go extinct from WNS, despite large, growing populations prior to WNS introduction [30]. Infection with the fungus increases rapidly during early winter when bats begin to hibernate, and prevalence reaches 100% in multiple species at most sites [31,32]. Mortality from WNS occurred 70–100 days after infection in laboratory studies, and in the field mortality peaks between January and April in the northeast USA, when pathogen loads on bats are highest [28,29,32]. After bats emerge from hibernation in the summer, they clear *P. destructans* from their skin surfaces, but the fungus can persist in hibernacula environments for long periods of time in the absence of bats, owing to its likely origins as a soil saprotroph [33–37]. Therefore, when bats return to hibernacula in the fall, *P. destructans* can continually re-infect bats [31,32,34]. WNS appears to be endemic to Eurasia [38,39], and bats in Asia bats have lower levels of *P. destructans* infection, which may indicate increased resistance [15].

Despite widespread declines and extirpation of many colonies in North America, some colonies in New York of one species, the little brown bat (*Myotis lucifugus*), now appear to be persisting, but by unknown mechanisms [30,40–43]. New York bats initially declined sharply from disease (figure 1), but some colonies have subsequently stabilized at 5–30% of their original size [30,40]. The severe declines have imposed very strong selection pressure on bats to persist with the fungus [44].

We examined support for four potential mechanisms of persistence by fitting a multi-compartmental, susceptible-infected model to data on prevalence and infection intensity (figure 2). We compared infection dynamics in stabilized post-epidemic populations from New York to colonies in the mass mortality phase of WNS. Comparison of data, models and parameter values allowed us to differentiate between differences in resistance, tolerance or changes in transmission between stabilized and declining populations.

2. Material and methods

(a) Sample collection and analysis
We collected data on population and infection dynamics of hibernating little brown bats at nine colonies (figure 1), including four
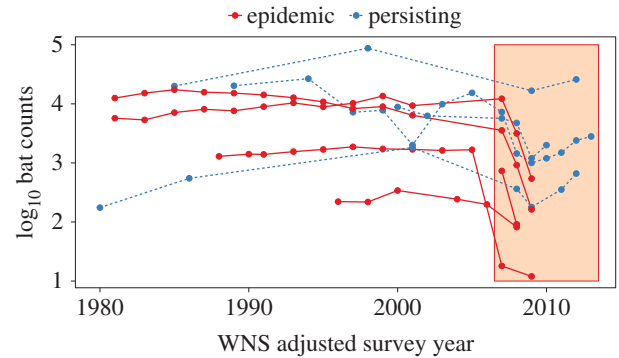

Figure 1. Winter counts of hibernating little brown bats from 1980 to 2013 in three states (New York: blue, dashed line—persisting; Illinois and Virginia: red, solid line—epidemic) with the red box indicating the presence of WNS. Survey year was standardized across sites by deducting the difference between 2007 and the year of WNS arrival from the survey year for each site.

persisting sites in New York, and five epidemic sites in Illinois (two sites sampled over two years) and Virginia (three sites). Persisting sites all had positive annual population growth rates, whereas epidemic sites had annual declines of 50–90% in the year of sampling [30,31]. All sites were sampled at least twice during each season, but sampling was limited to a maximum of three times per winter to reduce disturbance to hibernating bats [45]. Hibernating populations were censused by searching the entire site and counting all bats by species. In New York and Virginia, counts were done once per year (but not every year) from January to March by researchers and state agency personnel. In Illinois, bats were counted once per year before WNS detection and twice per year afterward, during early (November) and late (March) hibernation. Repeated surveys of the same populations suggest that uncertainty in the counts is approximately normally distributed with a coefficient of variation of approximately 11%. All research was conducted under approved protocols 11-022 by the IACUC of Boston University or #Frickw1106 by the IACUC of University of California Santa Cruz.

We collected epidermal swab samples from a mean of 19 little brown bats at each site to determine presence and intensity of *P. destructans* infection. We sampled bats by rubbing a polyester swab moistened with sterile water five times each across bat forearms and muzzles [46]. Samples were stored in RNAlater for preservation until DNA extraction. Samples were tested for the presence and quantity of *P. destructans* DNA using real-time qPCR [31,32].

(b) Modelling approach
We used a susceptible (*S*)-infected (*I*) continuous time compartmental model with three infected classes (I_1, I_2, I_3) to model the within-winter season infection and load dynamics of *P. destructans* on bats (equation (2.1)).

$$
\left.
\begin{aligned}
\frac{dS}{dt} &= \frac{-\beta S(I_1 + I_2 + I_3)}{N}, \\
\frac{dI_1}{dt} &= \frac{\beta S(I_1 + I_2 + I_3)}{N} - \gamma_1 I_1, \\
\frac{dI_2}{dt} &= \gamma_1 I_1 - (\gamma_2 + \Delta\gamma_2)I_2 \\
\text{and} \quad \frac{dI_3}{dt} &= (\gamma_2 + \Delta\gamma_2)I_2 - \alpha I_3.
\end{aligned}
\right\}
\quad (2.1)
$$

Here, β is the transmission rate, γ is the transition rate from one load class to the next (e.g. fungal growth rate), $\Delta\gamma$ is the difference in growth rates between epidemic and persisting populations (γ_{epi} and γ_{pers} in figure 2), α is the disease-caused
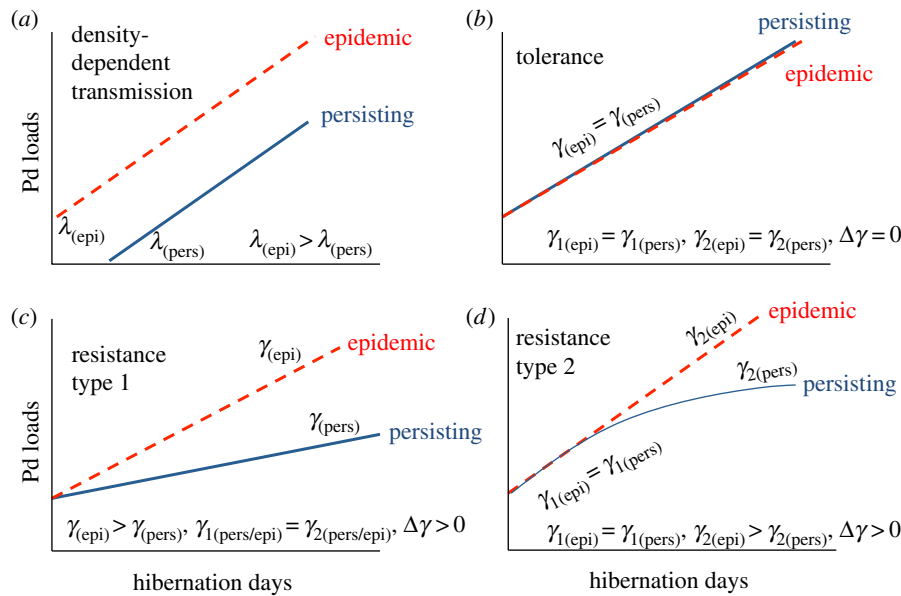
Figure 2. Hypothesized patterns of fungal loads or infection intensity of *P. destructans* (Pd) under different mechanisms of persistence for little brown bat populations. (*a*) *Density-dependent transmission*: Here, the force of infection (λ, the probability of a susceptible individual becoming infected per unit time) is higher in epidemic (epi) populations than in persisting (pers) populations. A higher λ in epidemic populations would result in these bats becoming infected earlier in the hibernation season, and reaching higher loads than bats in persisting populations at the time of sampling. (*b*) *Tolerance*: fungal growth on bats (γ) is identical between persisting and epidemic populations, but no mortality occurs in persisting populations, therefore $\Delta\gamma$ (the difference in fungal growth rates between persisting and epidemic populations) is 0. γ_1 is the fungal growth rate at low loads (between lower and medium load classes) and γ_2 is the fungal growth rate between medium and high load classes. (*c*) *Resistance type 1*: fungal growth on bats is lower across all loads in persisting populations than in epidemic populations. (*d*) *Resistance type 2*: fungal growth on bats is initially similar to growth rates on bats in epidemic areas, but loads asymptote at moderate levels.

death rate and N is the total colony size. We have assumed that transmission is frequency dependent based on the clustering behaviour of bats that would be expected to maintain a fixed number of neighbours across a range of densities [47,48], and the lack of evidence for density-dependent declines in this species [30]. We assumed that death only occurs in the highest load class, which is consistent with the long delay (70–100 days) between infection and mortality seen in laboratory infection studies [29] and field data [49]. We have not included a recovered class because there is no evidence that exposure to the fungus protects bats from repeated infection [32].

We fit the model to the data by assigning individuals to each class based on measured fungal loads: I_1, low loads (below $-4 \log_{10}$ ng), I_2, medium loads (between -4 and $-2 \log_{10}$ ng), and I_3, high loads (greater than $-2 \log_{10}$ ng). We initially built a model with three load classes as the simplest possible model that would enable us to test between resistance type 1 (figure 2; an overall reduced pathogen growth rate) and resistance type 2 (figure 2; a reduced pathogen growth rate only at higher fungal loads). Results were similar using a model with seven load classes (electronic supplementary material, figure S1). We chose seven load classes because it allowed us to divide individuals into a larger set of classes (and confirm that our selection of three load classes did not produce spurious results) without resulting in many load categories with zero bats. We assessed the evidence for a difference in tolerance or two types of resistance (figure 2) between epidemic and persisting sites by fitting a parameter, $\Delta\gamma$, that quantifies the difference in the transition rate, γ, between epidemic and persisting sites. For resistance type 1, we fit a parameter that quantified the overall difference in the transition rate for both load transitions (I_1 to I_2 and I_2 to I_3), reflecting an overall lower fungal growth rate (electronic supporting material, equation S2). For resistance type 2 (equation (2.1), above), we fit a parameter that quantified the difference in the transition rate for only the load transitions from I_2 to I_3. We compared the fit of these two models by comparing the fitted likelihoods, because both models had the same number of parameters.

We fit the model to the entire dataset (four persisting endemic sites and five declining epidemic sites, including two years of data for the two Illinois sites, with a total of 454 sampled bats divided into three load classes and susceptible individuals), simultaneously. We maximized the joint likelihood of the distribution of bats in the four infection classes (S, I_1, I_2, I_3) using a multinomial distribution, and the late-winter population counts from the Illinois sites using a Gaussian distribution. For the population counts, we used a Gaussian distribution with the mean equal to the actual count and a coefficient of variation of 0.11, based on a previous analysis of repeated counts of the same population. We fit the model using the *optim* function in R (v. 3.2.2) with the L-BFGS optimization algorithm and constrained all parameters to be greater than or equal to 0. We fit the model using the measured values for the fraction of individuals in each class at the first sampling point in each winter as the starting conditions. We assumed deviations between the model and data were owing entirely to measurement error, but we would have obtained similar results if we had fit both process and observation error because most sites had only two points in each time series.

3. Results

In the first year of pathogen invasion, the fraction of bats infected with *P. destructans* increased from zero in early winter to nearly 100% (figure 3; sites IL1 Year 1, IL2 Year 1). In subsequent years, bats became infected much earlier in hibernation, and early winter prevalence was already more than 50% in most colonies of both epidemic and persisting sites (figure 3, all other panels). Subsequently, at all but one site, most individuals were infected by the end of winter (figure 3).

Infection intensity increased over each winter, and at epidemic sites at least one year after pathogen invasion, fungal loads were almost uniformly high, with most individuals
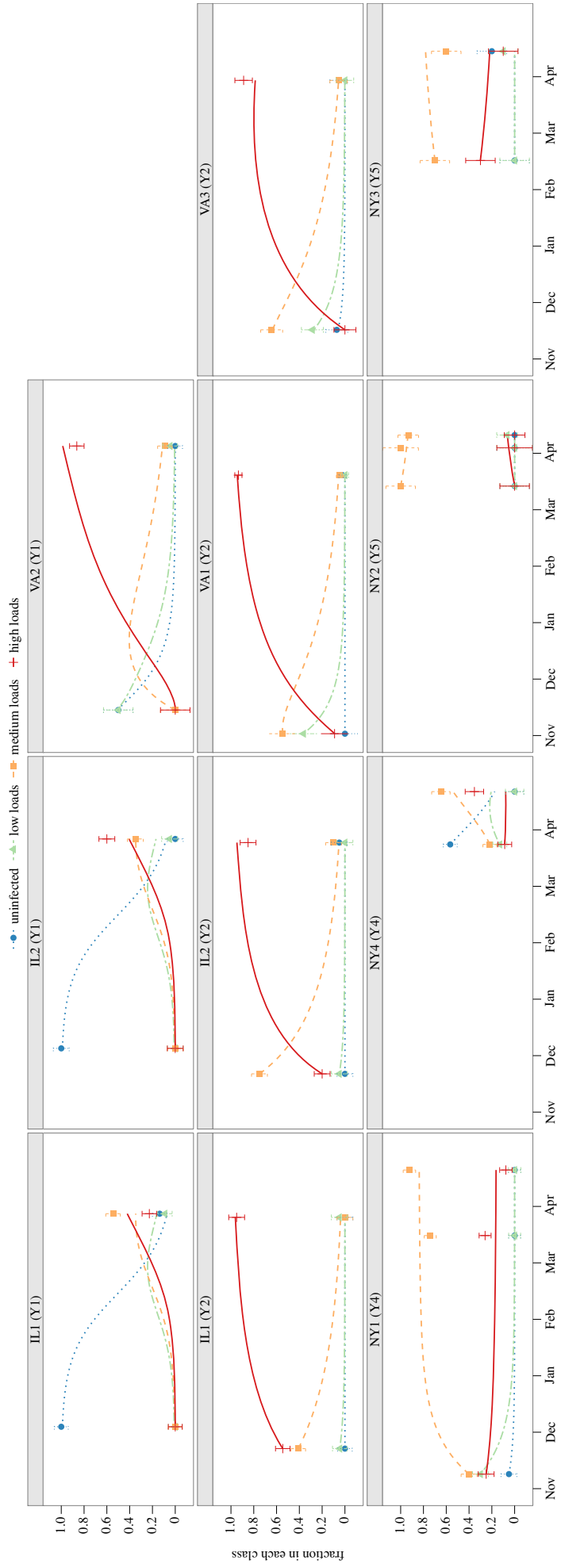
4

Figure 3. Model (lines) fit to bat fungal load data (points ± s.e.), from equations for resistance type 2. Dotted lines show fitted model for the frequency of uninfected bats, dot-dash lines show fitted model frequency of bats with low loads, long dash lines show fitted model frequency of bats with medium loads, and solid lines show fitted model of bats with high loads. Panel labels include the year after WNS arrival that the site was sampled (e.g. Y1 is the first year of WNS detection).
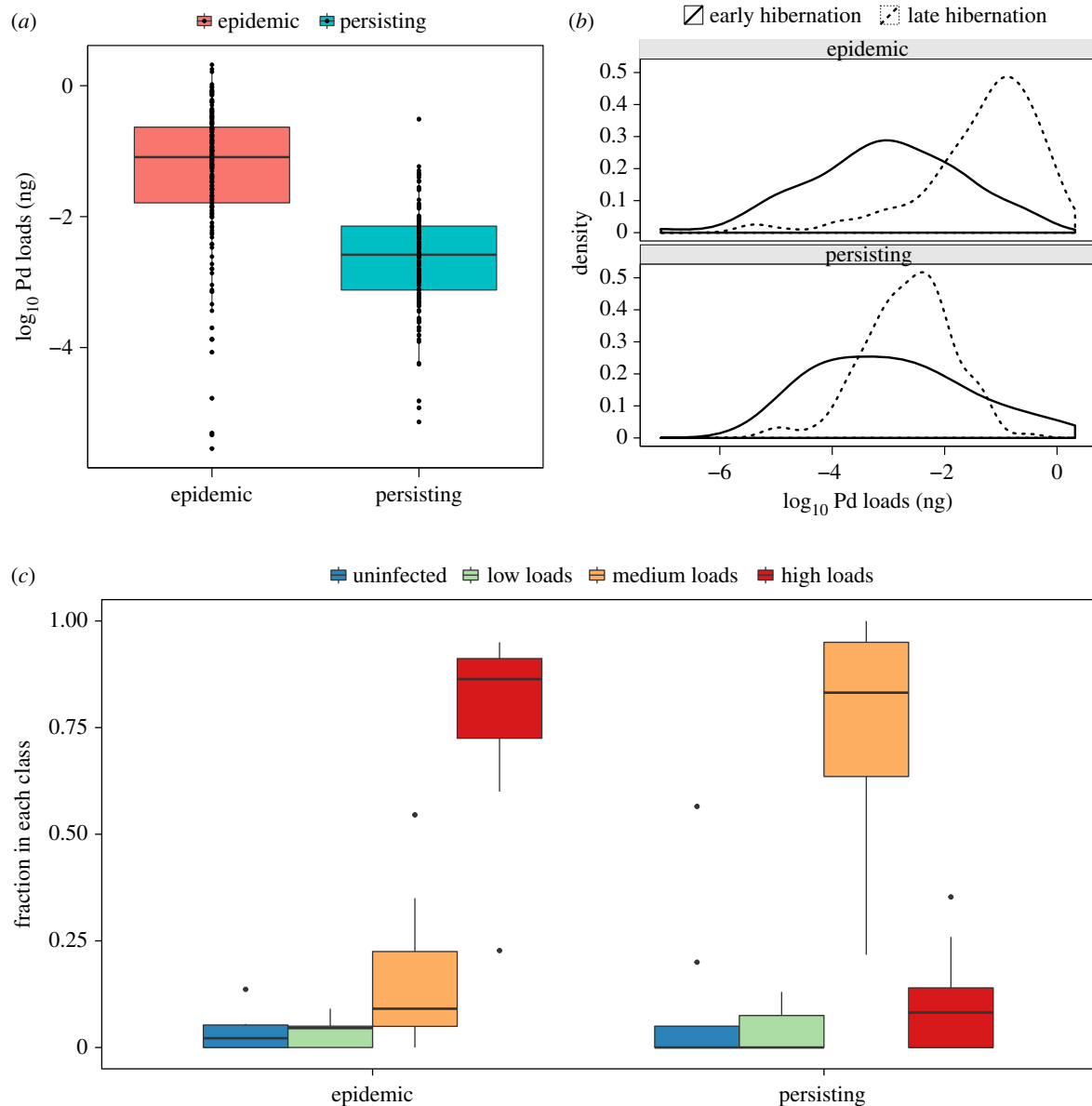
Figure 4. (*a*) Late-winter fungal loads of *P. destructans* (Pd) on individual bats at persisting and epidemic sites. Points are individual bats and the bold horizontal lines indicate the medians, the boxes encompass the 25th to 75th percentiles of the data, and the whiskers extend to points within 1.5 times the inter-quantile range. (*b*) Distribution of individual bat fungal loads during early (solid) and late hibernation (dashed) at persisting (NY) and epidemic sites (VA and IL). (*c*) Fraction of bats in each load class at the end of hibernation in epidemic and persisting sites. The bold horizontal lines indicate the median, and the boxes encompass the 25th to 75th percentiles of the data, as in panel (*a*). The dots indicate outlier points of the data.

having fungal loads in the 'high' load class (figures 3 and 4; electronic supplementary material, figure S1). By contrast, at persisting sites, late-winter loads were much lower, with most bats being in the 'medium' load class (figures 3 and 4; electronic supplementary material, figure S1). Overall, late-winter loads differed substantially between epidemic and persisting sites, with persisting sites having an average of 20-fold ($10^{1.3}$) lower fungal loads (linear mixed effects model: persisting sites fungal $\log_{10}$ load coeff.: 1.28 ± 0.30; $T = -4.3$; $p < 0.001$; figure 4*a*,*b*). Loads in early hibernation did not differ significantly between epidemic and persisting sites (persisting fungal load coeff.: 0.55 ± 1.3; $T = 0.43$, $p = 0.67$). The difference in the frequency distribution of bats in the different load classes between epidemic sites and persisting sites was similar whether we used three load categories (figure 4*b*), or seven (electronic supplementary material, figure S1).

Fitted models suggested that the difference in fungal loads between epidemic and persisting populations in late winter was owing to a reduction in growth rate between the last two load classes and not simply an overall lower growth rate (difference in log likelihoods: 26.6 or ΔAIC = 53.2, table 1; see the electronic supplementary material for model comparisons). Specifically, the best-fitting model had identical growth rates at low fungal loads between epidemic and persisting sites, whereas growth rates from moderate to high fungal loads were near zero at persisting sites (figure 5; γ_2 at persisting sites = 0.09), but almost the same as from low to moderate loads at epidemic sites (figure 5; electronic supplementary material, figure S2; γ_2 at epidemic sites = 1.13).

4. Discussion

Although all organisms are under continuous selective pressures from dynamic environments [50], the selective pressures exerted by human activities can be especially strong and sometimes result in much faster trait change than other natural processes [16,17,51]. The introduction of species to

Table 1. Evidence in support or against hypotheses in figure 2.

| hypothesis	supported	evidence
reduced transmission owing to density-dependent transmission	no	— colony sizes in persisting populations larger than epidemic sites — early hibernation fungal loads in persisting populations equal to or higher than epidemic populations
tolerance	no	— $\Delta\gamma \neq 0$ — late hibernation fungal loads were much higher in epidemic populations
resistance type 1	no	— $\Delta\gamma_2 > 0$; so $\gamma_{2(\text{epi})} > \gamma_{2(\text{pers})}$ and $\gamma_{1(\text{pers})} > \gamma_{2(\text{pers})}$ — loads in persisting populations were equal to epidemic populations in early hibernation but lower in late hibernation
resistance type 2	yes	— $\gamma_{1(\text{epi})} = \gamma_{1(\text{pers})}$ — $\gamma_{2(\text{epi})} > \gamma_{2(\text{pers})}$ — $\Delta\gamma_2 > 0$ — loads in persisting populations initially the same as epidemic but then asymptote, whereas fungal loads continue to increase in epidemic sites
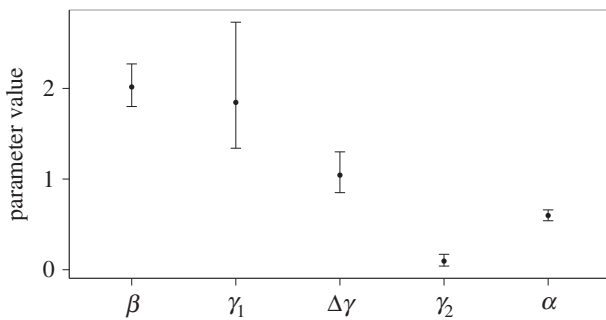
Figure 5. Estimated parameter values and 95% CIs. β is the transmission coefficient (*per capita* infectious contact rate per month), γ_1 is the transition rate between load classes I_1 and I_2, γ_2 is the transition rate between load classes I_2 and I_3 (*per capita* numbers of bats transitioning between loads classes per month), $\Delta\gamma$ is the difference in transition rate between the I_2 and I_3 classes between epidemic and persisting populations (i.e. the transition rate between the I_2 and I_3 classes for epidemic populations is $\gamma_2 + \Delta\gamma$) and α is the death rate from the third infected class, I_3 (*per capita* rate of bats dying per month).

new regions is one such activity that exerts strong selective pressure [52,53], and the introduction of pathogens to novel host communities is no exception [26]. WNS has caused severe declines in North American bats (more than 90% mortality in several species) and has thereby exerted intense selective pressure on bat populations to evolve traits to persist with this pathogen. We found that populations of one bat species that are now persisting with the pathogen have reduced growth of the fungus resulting in much lower fungal loads than bats at sites where declines are occurring. Although these data are from different populations and thus do not strictly demonstrate change in the same populations over time, the change in population trajectories at persisting sites and the differences in infection dynamics between persisting and declining sites suggest that the evolution of more resistant bats is a plausible explanation for population persistence. The large initial declines in New York are of the same magnitude as declines in epidemic sites (figure 1; [30]), suggesting a change in disease dynamics since initial invasion, and not that bats simply differed geographically.

The difference in fungal loads between persisting and declining bats indicates that persisting bats are not simply tolerant of the fungus, and is consistent with either resistance or density-dependent factors (table 1). Two lines of evidence suggest that reduced transmission at persisting sites owing to reduced densities is unlikely. First, all colony sizes of persisting sites are larger than all epidemic colony sizes. Second, fungal loads early in hibernation were as high or higher at persisting sites than declining sites, which is the opposite of what would occur if transmission was lower at persisting sites. Thus, the data are inconsistent with both tolerance and reduced transmission owing to density–density dependent transmission, but are consistent with host resistance.

Although the data suggest that bats at persisting sites are more resistant to growth of *P. destructans*, the form of resistance best supported by the data is not simply a reduction in pathogen growth rate (type 1 in figure 2 and table 1). There was no evidence that fungal growth rates were lower at low loads in persisting populations, whereas fungal growth was essentially halted at higher fungal loads. This is at odds with observing lower overall fungal growth rates that could be caused either by environmental factors influencing pathogen growth, such as temperature [54], changes in intrinsic pathogen growth rate, or load-independent host resistance traits. The pattern of resistance we observed (type 2 in figure 2) could be owing to changes in bat skin microbial communities resulting in a new carrying capacity of the fungus on endemic bats [55], host-induced reduction in resources for fungal consumption, increases in the time spent euthermic during late winter, an activation of an immune response when the pathogen reaches a fungal load threshold, or slow immune response activation by bats [56]. Regardless of which mechanism is responsible for the lower loads observed, our results suggest that resistance should increase bats' ability to survive through winter to reproduce in summer.

The type of resistance we observed—a reduction in maximum fungal loads without reducing initial growth—may put less selective pressure on the pathogen than an overall reduction in pathogen growth rate, and as a result, be less likely to select for higher replication rates by the pathogen. Our results indicate that bats at epidemic and persisting sites may reach

infectiousness (e.g. ability to transfer fungus to other bats) at similar times, and therefore transmission is more similar between epidemic and persisting populations than if resistance occurred by an overall reduction in fungal growth. The extensive environmental reservoir also contains strains of *P. destructans* shed by bats early in the WNS epidemic (and therefore not subjected to current selection pressures), and pathogen gene flow from the environmental reservoir as well as from bats at declining sites [31,57,58] may slow the speed of pathogen evolution.

(a) Knowledge gaps and future directions

Although resistance appears to be present at all four persisting populations we studied, three lines of evidence suggest that other populations of little brown bats, or other bat species, may persist owing to other mechanisms or may be driven extinct. First, little brown bat populations were much larger in the northeastern USA than in other places, possibly allowing greater genetic diversity on which selection could act [40,58]. Second, host–pathogen interactions may not be the same in all places. Specifically, at some sites the fungus may grow faster owing to warmer temperatures [30], resulting in individuals with limited resistance being unable to limit fungal growth below loads leading to death. Third, variation in resistance may not exist in species other than little brown bats. The Northern long-eared myotis (*M. septentrionalis*) has disappeared from all sites within four years of WNS detection [30,31,40], and strong evidence suggests this species may be driven extinct in the near future.

It is also unclear what mechanism causes resistance in persisting populations, and most importantly, whether this trait is heritable. If resistance is heritable and at least partly dominant, then translocations to regions where this species has nearly been extirpated might greatly speed population recovery [22,57]. Recent genetic evidence suggests that populations of little brown bats east of the Mississippi river were

panmictic before WNS [58], so gene flow between resistant and non-resistant individuals may slow evolution of resistance across eastern bat populations. Regardless, owing to the low reproductive potential of little brown bats (which have only one young per year) [47,59], it will be decades before this species can reach its pre-WNS abundance.

(b) Conclusion

Anthropogenically mediated introductions of pathogens have caused widespread mass mortality events [3,4,6], extinctions [60,61] and changes in community composition [9] and ecosystem function [10]. The persistence of many species in the Anthropocene will depend on the ability of these hosts to adapt to cope with pathogen introductions [62]. Less adaptable species will likely vanish, as has occurred with the Northern long-eared bat following WNS detection [30,32,40]. In order to preserve ecosystems, conservation efforts need to reduce continental shifts in pathogen distributions.

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